

# **Organic Stereochemistry**

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Professeur à l'Université de Paris-Sud

**Translated by M. C. Whiting  
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# Preface

Stereochemistry constitutes an area of chemistry itself, not a distinct science; but it is an area conveniently treated as a unit. Not long ago one would not have needed to prefix the title with the word 'organic', since stereochemistry was born within organic chemistry, and permeated by the ideas of organic chemistry. With the development of effective methods of studying the solid state, however, inorganic chemistry has developed a distinct and comparably large stereochemistry of its own, and is now better treated separately. The present edition of a book first published in France appears well suited to the education systems of the United Kingdom and the United States, making few assumptions about previous knowledge, but reaching a level of understanding that should suffice for any graduate student.

Stereochemistry derives from the work of Pasteur, perhaps more completely than chemistry itself from the work of Lavoisier. It was in French that van't Hoff wrote 'La chimie dans l'espace', a book that in 1875 brought his and Le Bel's appreciation of the tetrahedral carbon atom and its consequences to the attention of a rather sceptical world; a book that would have served adequately as a textbook of stereochemistry until, say, 1950. Contact with the continuing French tradition in stereochemistry could be valuable to an English-speaking chemist, and the translators do not apologise because the style and language of the original can be sensed in this often rather literal translation. They have, however, taken the chance to correct a few unimportant slips and misprints, and to add a few footnotes.

Some of the matters dealt with in this book, particularly conformational analysis and stereoisomerism, were dealt with in the *cours de D.E.A.* at the Université de Paris-Sud. We thank R. Bucourt, J. Weill-Reynall and C. Mazieres for their valuable advice in the editing of the French text.

1978

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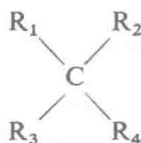
# Introduction

In the definition of stereochemistry it is helpful to remember that the prefix 'stereo' originates from the Greek root *stereos*, solid or volume. Stereochemistry is, therefore, 'chemistry in space'. This definition is that which was given by Le Bel and van't Hoff in 1874 when these authors advanced their famous hypothesis of the tetrahedral carbon atom. Such a definition would be completely erroneous if it were held to imply the existence of two chemistries, of which one was spatial. Chemical reactions, which imply an approach of reactants and the formation of a transition state, all take place in space in three dimensions. The molecules of which we are considering the structure are not completely defined by a planar formula, and it is necessary to specify the relative position of the atoms, one to another. Because of the progress of chemistry, stereochemistry and chemistry have become inseparable. Chemistry 'on paper', i.e. in two dimensions, making use only of planar structures, is completely inadequate when a chemical phenomenon, for example a reaction mechanism, is examined in detail. Molecular models and their symbolic planar representations are of great value to the chemist for predicting isomers and understanding reactions.

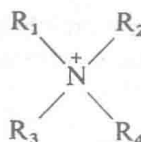
Stereochemistry thus places the emphasis on the steric aspect of chemistry, and valuable information is obtained by examining a reaction, however simple, from the point of view of stereochemistry.

Stereochemistry has played an important role in the development of chemistry. Crystallography enabled the chemists of the last century to become familiar with crystalline forms, which are related to the organization of the crystalline lattice and indirectly to the structure of the molecule. In 1848, Pasteur, due to his understanding of crystallography and his powers of observation, succeeded in separating two types of crystal of the sodium ammonium tartrate formed from racemic tartaric acid; one the mirror image of the other. This first resolution of a racemic compound made the world aware of a particularly important form of isomerism, optical isomerism. Thirty years later, Le Bel and van't Hoff made the optical isomerism of compounds

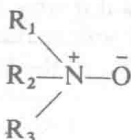




their main argument in eliminating the possibility that the four valencies of carbon were coplanar. In the particular case of carbon, structural theory was thus placed on a solid foundation. The arrangement of valencies around an atom of nitrogen was similarly studied by stereochemical methods. It was found that quaternary ammonium cations

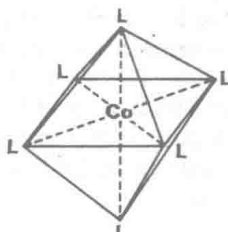


and amine oxides



could be obtained optically active. In these compounds therefore, nitrogen does not have a planar structure. This result was particularly interesting for studies on the semipolar bond  $\rightarrow N^+ - \bar{O}$ . Compounds of sulphur, phosphorus and arsenic were also examined by these techniques.

The chemistry of metallic complexes made considerable progress at the beginning of the century as a result of the work of Werner, for which the Nobel Prize was awarded. Werner put forward the revolutionary hypothesis of octahedral cobalt or nickel in complexes where these metals were hexacoordinate. The metallic atom is at the centre of an octahedron and the ligands are placed at the corners. This representation of chemical bonds around a metal has been particularly fruitful, and has allowed the prediction of all the isomers possible as a function of the nature of the ligand L.



There are many additional examples which demonstrate the essential role of stereochemistry in the evolution of the concepts of chemical bonding and reaction mechanisms.

Stereochemistry permeates all chemistry, whether it is described as inorganic, organic or physical. The frontiers between disciplines are difficult to define, and it is in any case undesirable to create divisions which can soon become sterile. There has recently been a rediscovery of inorganic chemistry by organic chemists, who have learned to carry out some remarkable organic syntheses by using catalysts based on organometallic complexes. Physical chemistry has yielded methods for studying molecules and their stereochemistry, and for throwing light on transient reaction intermediates. The use of physical methods in the last decade has revolutionized organic chemistry and profoundly changed its character.

As the aim of this book is to emphasize organic stereochemistry, its scope must first be defined. Inorganic chemistry will not be considered, although this has an important stereochemical aspect; the chemistry of boron, phosphorus, sulphur and transition metal complexes, for example. The book will be limited to conventional small organic molecules composed of carbon, hydrogen and various heteroatoms (oxygen, nitrogen, sulphur and phosphorus are among the most frequent), although organic macromolecules and the stereochemical problems posed by biochemistry will also be examined superficially. It must, however, be noted that, in these latter branches of organic chemistry, structural and stereochemical aspects play an increasingly important role.

The apparent division of chemistry has been emphasized. This division has become more and more evident, because of the importance of experimental methods which are related to the nature of the compounds studied. Naturally the methods one uses vary according to whether one is trying to isolate a gas, a water-soluble compound (e.g. a salt or an amino acid) or a compound soluble in an organic solvent, or whether one wishes to study the chemistry of the solid state. But this great diversity of chemistry fortunately does not imply an extreme specialization for the chemist himself, if he can raise himself above the descriptive and technical aspects, which are important but not essential. For example, the conformational analysis of hydrogen peroxide,  $\text{HO}-\text{OH}$ , or of ethane,  $\text{H}_3\text{C}-\text{CH}_3$ , and of their derivatives, proceeds by the same principles and makes use of the same concepts.

In all branches of chemistry, it is evident that there are two aspects of stereochemistry; static and dynamic.

*Static stereochemistry* deals with the structure of molecules, that is to say the relative positions of atoms in space. Frequently a molecule is not rigid, and its shape can vary according to the temperature or the nature of the substituents. These variations are generally due to rotations about single bonds and are studied with the aid of conformational analysis

Stereochemistry allows one to predict the number of stereoisomers corresponding to a planar formula, i.e. to a given sequence of atoms. Methods have been perfected for studying the stereochemistry of molecules. In the chemistry of natural products these methods are essential for the complete definition of the structure of an isolated compound. The interest of such a determination is not purely academic; the repercussions are considerable if the substance possesses therapeutic activity and knowledge of its structure makes a partial or total synthesis possible on an industrial scale. Cortisone is an example; there were only a few milligrams of cortisone in the world in 1945, its anti-inflammatory action was discovered in 1947, and its partial synthesis from the bile acids was carried out in 1950 on a kilogram scale.

*Dynamic stereochemistry* deals with the reactivity of molecules. Understanding the steric course of a reaction implies understanding the stereochemistry of the products formed and, if possible, the course of the reaction and the geometry of the transition state. Stereospecificity should be a characteristic of a modern organic synthesis. It always constitutes a difficult problem, which belongs to the field of dynamic stereochemistry. As an example of the importance of steric control in synthesis, it can be calculated that a compound of which the planar formula contains three asymmetric carbon atoms, for example penicillin, can exist in the form of  $2^3 = 8$  distinct stereoisomers, but only one isomer possesses the desired antibiotic activity. The study of dynamic stereochemistry is a necessary means for obtaining precise information on reaction mechanism (ionic, radical, photochemical and even enzymatic reactions). A well-known example is the Walden inversion (see Chapter 5). As early as 1903 Walden had shown while working with optically active molecules that in certain cases of nucleophilic substitution, now called  $S_N2$ , an inversion of configuration occurred which implied a reversal of the initial tetrahedron:



In this book organic stereochemistry will be developed progressively. In Chapter 1 the electronic properties of atoms which constitute organic molecules will be revised. These comprise the basic parameters (inter-valency angles, interatomic distances, orbitals, etc.) which to a large extent constrain the geometry of the molecule.

Chapter 2 presents molecular models and methods of representing molecules.

Conformational analysis, described in Chapter 3, allows molecular structures to be analysed when there are possibilities of rotation around certain bonds. The shape of a molecule is then susceptible of considerable variation; some conformations are much more stable than others, and chemical reactivity is related in most cases to molecular conformation.

In Chapter 4, different types of stereoisomerism are reviewed. Finally, dynamic stereochemistry is treated in Chapter 5.

We hope that at the end of this work we will have succeeded in giving the reader some insight into one of the recent trends in modern organic chemistry.

# Molecular geometry and chemical bonding

It is usual to define organic chemistry as the chemistry of carbon compounds. Organic compounds always contain carbon and usually hydrogen; very often heteroatoms such as oxygen, nitrogen, sulphur, phosphorus, the halogens or alkali metals are also present.

The great wealth of organic chemistry has several causes. The stability of covalent C—C and C—H links is an essential factor, allowing the synthesis of complex chains of carbon atoms. The quadrivalence of carbon permits structural isomerism by multiplying the possible arrangements of atoms. The non-coplanarity of the valencies issuing from a tetragonal carbon atom, and the planarity of an ethylenic double bond, give rise to stereoisomers. Stereochemistry begins with the characteristic properties of the linkages formed between the atoms which constitute a molecule. Before considering the geometry of simple molecules it is therefore necessary to discuss the nature of chemical bonds.

## Revision of the theory of chemical bonding

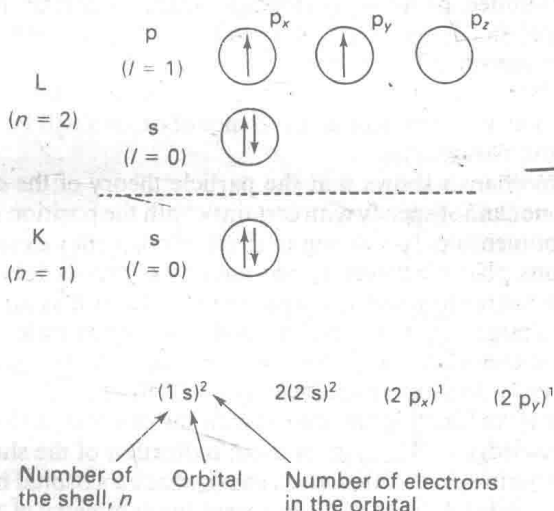
The bond formed between atoms makes use of their outer electrons. It is no longer conceivable to consider the problem of the chemical bond without a quantitative treatment of the energies and spatial distributions (or their equivalent) of the molecular orbitals occupied by the bonding electrons. It will be dealt with here by a simplified approach, which will suffice for the many structural problems of organic chemistry.

Electrons are arranged around each atom in shells (K, L, M, etc.), each shell being divided into subshells (s, p, d, f), themselves subdivided into orbitals containing at the most two electrons of opposed spin.

To determine the number of outer electrons of an atom it is necessary to know the total number of electrons of that atom (equal to its atomic number  $Z$ ) and the rules for filling electronic shells. These rules are based on the fact that an electron, characterized by four quantum numbers, must be different from all other electrons (the Pauli principle). The principal quantum number  $n$  defines the shell:  $n=1$ , shell K;  $n=2$ , shell L, etc. The secondary quantum number  $l$  differentiates the subshells and can

take the values between 0 and  $(n-1)$ :  $l=0$ , subshell s;  $l=2$ , subshell p, etc. The magnetic quantum number  $m$  (possible values from  $-l$  to 0 to  $+l$ ) introduces the division into orbitals in which the electron can have spin states  $+\frac{1}{2}$  or  $-\frac{1}{2}$  (indicated by  $\uparrow$  or  $\downarrow$  to symbolize electrons with rotations in opposite directions).

Consider, as an example, the electronic configuration of a carbon atom ( $Z=6$ ), assumed to be 'free'. The most stable orbitals are filled first, that is to say going outward progressively from the nucleus. In Figure 1.1 the distribution of the six electrons is represented in two equivalent ways. Note that the p electrons are situated in two orbitals rather than in the same orbital, according to Hund's rule, which predicts greater stability for this distribution.



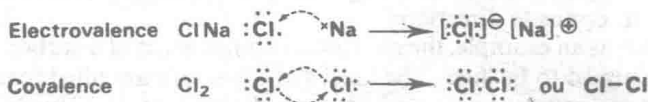
**Figure 1.1** Electronic configuration of the carbon atom in its ground state

In discussing the chemical bond only the outer electrons of the atom need be considered. As a result of the behaviour of these electrons, bonds can show all characteristics intermediate between the two extreme cases which are commonly called electrovalence and covalence.

The electrovalent bond is common in inorganic chemistry. Conceptually it is very simple: electrostatic attraction binding two ions of opposite charge. These ions are formed by the exchange of one or more electrons between two atoms. The atom which loses an electron becomes a cation, the atom which accepts an electron becomes an anion.

In the covalent bond each atom is at the same time a donor and an acceptor of an electron. The bond is constituted by the sharing of two electrons, which become the doublet of the bond.

The diagrams of G. N. Lewis give a simplified representation of ions and molecules. In these diagrams only the peripheral electrons are considered, grouped, when possible, as doublets.



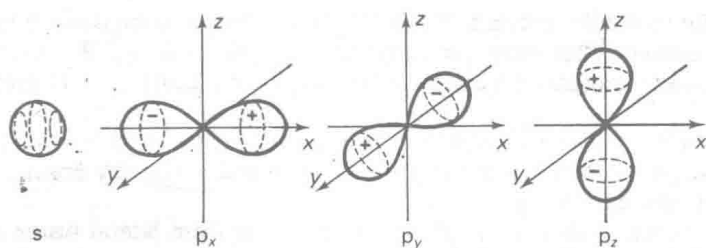
Very often the transfer of electrons leads to atoms surrounded by an octet of electrons, electronic structure  $s^2p^6$ . An octet of electrons is a factor for stability, which in particular characterizes the rare gases.  $\text{Cl}^-$  and  $\text{Na}^+$  are surrounded by an octet (for  $\text{Na}^+$  there is also an inner shell not represented). In  $\text{Cl}_2$  one can equally consider that each chlorine atom contains eight peripheral electrons. The distribution of electrons in the L shell of carbon, Figure 1.1, allows us to predict a bivalent character for this atom. The well-known quadrivalence of carbon will be explained in the following paragraphs.

Quantum mechanics shows that the particle theory of the electron is incomplete; one cannot specify with certainty both the position of an electron and its momentum. It is wrong to think of covalency as represented by two electrons, placed between two atoms and shown as dots in Lewis's diagrams. It is nearer to reality to represent the electron as an electronic cloud of total charge  $-e$ . This cloud has a density which varies according to the position considered and this electronic density, or the density of the probability of finding the electron, is equal to  $|\Psi_{(x,y,z)}|^2$ .

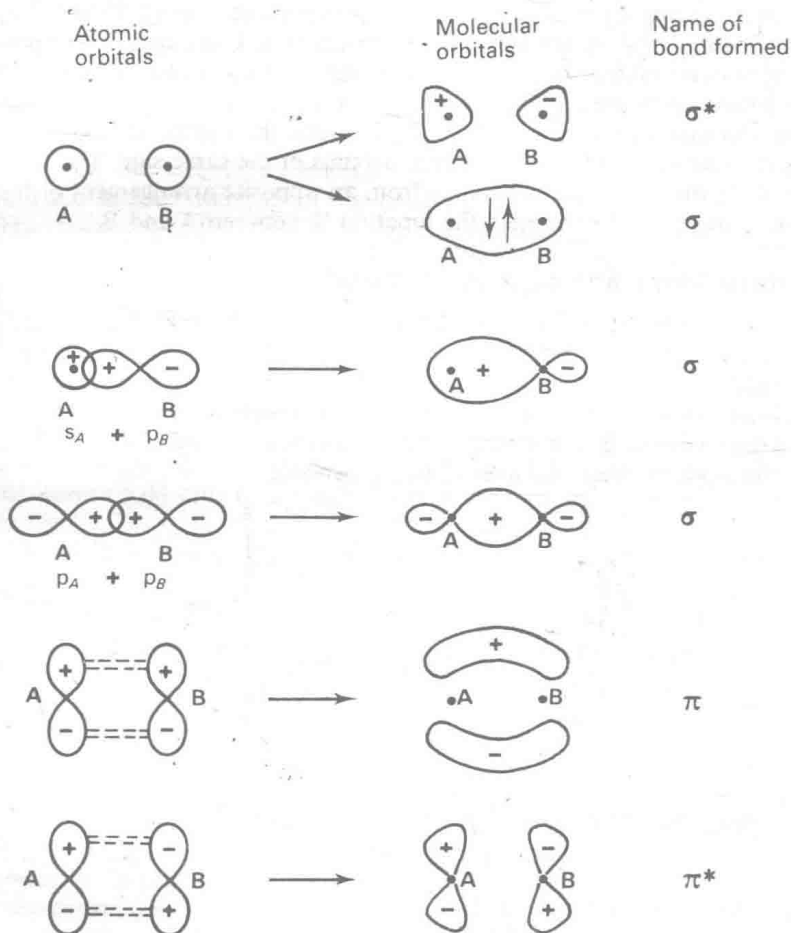
$\Psi_{(x,y,z)}$  is the wave function associated with the electron, also called the orbital. A knowledge of  $\Psi_{(x,y,z)}$  gives us an indication of the shape of the electronic charge in space. Calculation shows that an s orbital has spherical symmetry, while the three p orbitals have the symmetry of revolution around an axis, the axes being perpendicular to each other. The size of the electron cloud increases as shells become successively more distant from the nucleus, but the shape remains unchanged. Starting from the functions  $\Psi$  it is possible to plot the electronic density by calculating  $|\Psi|^2 dv$ . The greatest part of the electronic cloud, particularly the regions of high density, is localized in a volume having essentially the same symmetry as that of  $\Psi$ . Figure 1.2 shows a simplified but convenient representation of the electronic clouds s and p (called, incorrectly, orbitals). The sign of  $\Psi$  allows one to introduce the consideration of symmetry, which is one of the main features of present-day structural chemistry.

The covalent bond is discussed in quantum mechanics in terms of the overlap of atomic orbitals. Some stereochemical consequences are immediately predictable.

Figure 1.3 shows different cases of overlap of atomic orbitals. In every case a linear combination of orbitals  $\Psi_A$  and  $\Psi_B$  gives two possible solu-



**Figure 1.2** Schematic representation of orbitals (calculated from  $|\psi_{(x,y,z)}|^2$ )



**Figure 1.3** Overlap of atomic orbitals: formation of  $\sigma$  and  $\pi$  bonds



tions for molecular orbitals:  $\Psi$  and  $\Psi^*$ . The molecular orbital which tends to accumulate electronic charge between the atoms A and B is called a bond, and is occupied by two electrons if the molecule is in its ground state.

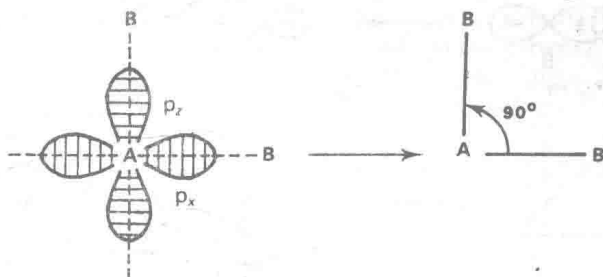
The  $\sigma$  bond always results from an axial overlap for the p orbital, ( $s_A + p_B$  or  $p_A + p_B$ ). The  $\sigma$  bond possesses cylindrical symmetry around the interatomic axis A—B.

The bonding molecular orbital which results from lateral fusion of p orbitals is very different. The electronic density is zero along the axis A—B, the electronic cloud being concentrated on either side of this axis ( $\pi$  bond).

In diagrams representing orbitals (the representation of  $\Psi$  or  $\Psi^2 dv$ ) it is essential to show the sign of the wave function. These signs are important in determining the steric course of many reactions (see Chapter 5). Calculations require the formation of a bonding molecular orbital, with the accumulation of electron density between the atoms, to take place by the overlap of regions of atomic orbitals of the same sign. The anti-bonding molecular orbital results from an opposite arrangement of the signs, and tends to diminish the function  $\Psi$  between A and B.

### Intervalecy angles, hybridization

The theory of the chemical bond makes possible the prediction of intervalency angles. It has been shown that a  $\sigma$  bond, in which a p atomic orbital participates, possesses rotational symmetry about the axis of this orbital. An atom A which can form two  $\sigma$  bonds from two p orbitals is characterized, in consequence, by an intervalency angle of  $90^\circ$ , which is the angle between the axes of two p orbitals.



Let us take, as examples, oxygen and sulphur:

O ( $Z=8$ )

configuration  $(1s)^2(2s)^2(2p_x)^2(2p_y)^1(2p_z)^1$ ;

S ( $Z=16$ )

configuration  $(1s)^2(2s)^2(2p)^6(3s)^2(3p_x)^1(3p_y)^1(3p_z)^1$ .